REMARKS

The specification has been amended to make proper reference to U.S. Patents that have issued from the applications listed in the specification as filed.

Claims 55-58 have been cancelled as being directed to a non-elected invention. Applicants specifically reserve the right to pursue the subject matter of the cancelled claims in one or more continuation or divisional applications.

Amended claim 34 is directed to a method of treating tumors in a mammal by normalizing the prolactin profile of the mammal and subjecting the tumor to photodynamic therapy (PDT). Support for amended claim 34 is found in the claims as originally filed.

CLAIM REJECTIONS

Rejections under 35 U.S.C.§112, first paragraph. Claims 34-54 are rejected under 35 U.S.C. §112, first paragraph. The Examiner contends that the specification does not reasonably provide enablement for treating cancer via photodynamic therapy (PDT) with all benzophenoxazine analogs, does not specifically define what is included or excluded as a benzophenoxazine analog, and that it cannot be predicted that any and all benzophenoxazine analogs, including those yet to be discovered, could be made and/or used to successfully treat tumors in PDT. The Examiner alleges it would require undue experimentation for one of relative skill in the art to practice the invention as claimed. Applicants respectfully traverse.

Amended claim 34 is directed to treating tumors with the combination of neuroendocrine resetting therapy and PDT. PDT is practiced with a benzophenoxazine-analog photosensitizer effective in PDT. The combined treatment eradicates or retards the growth of the tumor. Applicants submit that the specification is fully enabling for a benzophenoxazine analog

of proven effectiveness in PDT, as at the time the invention was made it was routine for those skilled in the art to determine which benzophenoxazine analogs were effective in PDT. In support of this statement, Applicants submit herewith an article by Cincotta et al. ("Novel red absorbing benzo[a]phenoxazinium and benzo[a]phenothiazinium photosensitizers: *in vitro* evaluation", Photochemistry and Photobiology, 46:751-758, 1987) which discloses the photochemotherapeutic properties of a series of nine benzophenoxazines. The benzophenoxazines were evaluated *in vivo* in cell culture for phototoxic effects on six different cell lines. Using the methods described in Cincotta et al., one of ordinary skill in the art could readily determine the benzophenoxazines that would be useful in practicing PDT. Such testing would be considered routine. Accordingly, at the time the invention was made, the specification was enabling for the full scope of benzophenoxazine analogs encompassed by amended claim 34 and its dependent claims 35-54.

Claims 34-54 are also rejected based on the Examiner's allegation that the specification does not reasonably provide enablement for a method for arresting the growth of or eradicating every type of tumor with the combination of neuroendocrine resetting therapy and PDT. Applicants respectfully traverse.

The Examiner alleges that it would not be predictable that all tumors would be responsive to PDT and neuroendocrine resetting because there are several instances where tumors actively secrete prolactin enhancers. In response, applicants note that amended claim 36 is directed to resetting the daily prolactin rhythm of a tumor bearing mammal to approach the daily prolactin rhythm of a normal mammal of the same sex and species by administering either a prolactin enhancer or a prolactin inhibitor. Such treatment would be effective in resetting the

prolactin rhythm in all subjects, including subjects bearing tumors which actively secrete prolactin enhancers. Such treatment is also commensurate in scope with the specification, which teaches resetting prolactin rhythms by administering either a prolactin enhancer or prolactin inhibitor.

The Examiner alleges further that the specification is not enabling for practicing the combination of PDT and neuroendocrine resetting therapy with hormone sensitive tumors, such as breast and prostate. Applicants respectfully traverse.

The present specification provides a disclosure that permits those of ordinary skill in the art to practice combined neuroendocrine resetting therapy and PDT, as called for in the present claims, on any malignant tumor. The specification discloses detailed methods for determining and modifying the daily prolactin rhythm of any tumor bearing mammal. The disclosure sets forth specific dosages of prolactin enhancers or reducers to be used in neuroendocrine resetting therapy and the proper times for administering dosages of a prolactin enhancer or reducer (*see* specification at page 16, line 9 through page 20, line 17). Detailed methods for practicing PDT are also disclosed in the present specification (*see* page 24, line 21 through page 26, line 26), including disclosure of different photosensitizers effective in PDT, and the wavelengths, durations and intensities of light required to effectively activate these photosensitizers.

The specification further discloses treatment of mouse EMT-6 cell tumors as an example of the efficacy of combined neuroendocrine resetting therapy and PDT. Figure 5 clearly shows that the combination of neuroendocrine resetting therapy and PDT has a synergistic effect in reducing tumor size, compared to either therapy alone.

The EMT-6 cell tumor model is a well established model system of tumorogenesis. At the time the invention was made, one of ordinary skill in the art would have expected the results obtained with EMT-6 cells to be applicable to other tumor cell types regardless of origin. Furthermore, using the information set forth in the present specification, one of ordinary skill in the art could make routine adjustments to the precise protocol of resetting prolactin rhythms (e.g., dosage of prolactin enhancer or reducer, timing of administration, *see* pages 16-23) and the precise protocol of PDT (e.g., choice and dose of benzophenoxazine analog, *see* pages 24-26) to optimize the synergistic effect obtained by combining the two treatments.

All of the information needed to practice the full scope of the present claims is found in the present specification. One skilled in the art would be able to practice the present claims without any further information. In fact, using the methodologies disclosed in the present application (and defined by the present claims), every tumor type tested to date has demonstrated a synergistic response (e.g., by reduction or eradication of tumor mass) when it has been exposed to the combination of neuroendocrine resetting therapy and PDT. Examples of such results are reported in the enclosed reference (Cincotta et al., Chronobiology International, 16(Supp)1: 21, 1999, abstract).

Claims 34-54 are further rejected on the grounds that the specification does not reasonably provide enablement for a method of treating cancer via PDT with prolactin enhancer at any time. The Examiner alleges that one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to the treatment of cancer with PDT in combination with the prolactin enhancer which is administered at any time during a 24

hour period. These grounds for rejection are not believed to be well taken and are respectfully traversed.

Amended claim 34 would not encompass administration of a prolactin enhancer at any time during a 24 hour period. Rather, amended claim 34 is drawn to administration of a prolactin enhancer or inhibitor at the particular time of day such that the administration results in resetting the prolactin profile of a tumor bearing mammal to approach the daily prolactin rhythm of a normal mammal of the same species and sex. Methods for determining the amounts and timing of administration of prolactin enhancer or inhibitor to effect resetting prolactin rhythms are set forth in detail (*see* pages 16-24). Accordingly, amended claim 34 is believed to be commensurate in scope with the specification.

In light of the above amendments and remarks, Applicants submit that the specification is enabling for the full scope of the claims. Accordingly, Applicants request withdrawal of all rejections under 35 U.S.C.§112, first paragraph and reconsideration of the claims.

Rejections under 35 U.S.C.§112, second paragraph. Claims 34-54 are rejected as indefinite. The Examiner contends that claim 34 and all claims depending thereon are incomplete for omitting essential steps, such omission amounting to a gap between the steps. In response, applicants have amended claim 34 to recite specific steps comprising the claimed method. Amended independent claim 34 and claims 35-54, which depend either directly or indirectly thereon, are believed to meet the strictures of 35 U.S.C. §112, second paragraph for definiteness, thus obviating this objection.

Claims 43-48 are rejected as indefinite for reciting "benzophenoxazine analogs".

The Examiner contends that the specification does not define what an analog of benzophenoxazine is and that the term does not have an art-recognized meaning. The Examiner alleges further that the specification does not include a limiting definition of benzophenoxazine analog. Applicants traverse on the grounds that "benzophenoxazine analogs", as described in the specification and understood by one of ordinary skill in the art, fully satisfies the requirements for definiteness set forth in 35 U.S.C. §112, paragraph 2, (*see* MPEP 2171).

Benzophenoxazine is a standard chemical compound whose constituents and activity are well known by those skilled in the art. Accordingly, one skilled in the art would understand the term "benzophenoxazine analog" to encompass any compound comprising a benzophenoxazine group and exclude any compound lacking such group. Examples of benzophenoxazine analogs are described in U.S. Patent No. 4,962,197 to Foley et al., which is properly incorporated by reference into the specification at page 23, lines 11-12. Furthermore, the benzophenoxazine analogs of amended claim 34 are restricted to those benzophenoxazine analogs that are effective in PDT. Methods for determining benzophenoxazine analogs that are effective in PDT were simple and routine at the time the invention was made (see attached reference: Cincotta et al., "Novel red absorbing benzo[a]phenoxazinium and benzo[a]phenothiazinium photosensitizers: *in vitro* evaluation", Photochemistry and Photobiology, 46:751-758, 1987). Accordingly, Applicants respectfully submit that, as required by 35 U.S.C.§112, second paragraph, amended claim 34 particularly points out and distinctly defines the metes and bounds of the subject matter that will be protected by the claim, and further sets forth the subject matter that Applicants regard as their own.

In light of the above remarks, Applicants respectfully submit that the claims are

definite. Accordingly, applicants request removal of all rejections under 35 U.S.C §112, first and second paragraphs, and reconsideration of the claims.

Rejections under 35 U.S.C.§102 and 103. Claim 34 is rejected as being anticipated by or, alternatively, obvious over Werning et al. (Arch. Ontolaryngol. Head Neck Surg., July 1995, v121, pp. 783-789) as evidenced by Molitch (Endocrinol. Metab. Clin. North Am., 1992 v21(4), ABSTRACT). Claims 34-54 are rejected as obvious over Lissoni et al. (Cancer, 1994, v73(3), pp. 699-701) and Bartsch et al. (Ann. NY Acad. Sci., 1994, v719, pp. 502-525) in view of Cincotta et al. (Cancer Research,1993, v53, pp. 2571-2579) and Cincotta et al. (Cancer Research,1994, v54, pp. 1249-1258).

Claim 34 has been amended to include the steps required to perform prolactin resetting therapy in a tumor bearing mammal, i.e., comparing the daily plasma prolactin profile of the tumor bearing mammal to a normal daily prolactin profile for healthy mammals of the same species and sex and adjusting the daily plasma prolactin profile of the tumor bearing mammal by administering a prolactin enhancer or prolactin inhibitor at appropriate time intervals of day such that the adjusted daily plasma prolactin profile of the tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy members of the same species and sex.

The prior art of record does not teach or suggest the steps for prolactin resetting therapy recited in amended claim 34. The prior art of record does not teach or suggest that the daily prolactin rhythm of a tumor bearing mammal should be compared to a healthy animal of the same species and sex. Nor does the prior art of record teach or suggest that the daily prolactin rhythm of the tumor bearing mammal should be modified to conform or approach the daily

prolactin rhythm of the healthy animal by-administering a prolactin enhancer or prolactin inducer. Accordingly, the prior art of record does not teach or suggest that these steps be practiced in conjunction with PDT, as claimed in amended claim 34. Amended claim 34 is therefore neither anticipated nor made obvious by the prior art of record. As each of the other pending claims 35-54 depends either directly or indirectly from claim 34, and therefore incorporates all of the attributes and limitations of claim 34, these dependent claims are also neither anticipated nor made obvious by the prior art of record. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1600 (Fed. Cir. 1988).

In light of the amendment to claim 34 and the above remarks, Applicants respectfully submit that claims 34-54 are free of the prior art of record. Accordingly, Applicants request withdrawal of all rejections under 35 U.S.C.§102 and 103 and reconsideration of the claims.

CONCLUSION

Applicants respectfully request entry of the above amendments and remarks.

In view of the above amendments and remarks, this application is believed to be in condition for allowance, which is earnestly solicited.

Respectfully submitted,

Mitchell Bernstein, Ph.D.
Registration No. 46,550
Agent for Applicants

DARBY & DARBY
805 Third Avenue
New York, NY 10022
(212) 527-7700

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Anthony H. Cincotta, et al.

Serial No.: 09/187,768 Art Unit: 1642

Filed: November 6, 1998 Examiner: G. Nickol

For: GROWTH INHIBITION AND ERADICATION OF SOLID TUMORS USING NEUROENDOCRINE RESETTING THERAPY AND PHOTO DYNAMIC THERAPY

MARK-UP FOR AMENDMENT OF MARCH 12, 2001
PURSUANT TO 37 C.F.R. § 1.121

March 12, 2001

IN THE SPECIFICATION

First paragraph immediately after the title:

This is a continuation of Application Serial No. 08/838,079, filed April 15, 1997, now abandoned, which claims priority from provisional application No. 60/016,619, filed May 1, 1996 under 35 U.S.C. 119. Each of these prior applications is hereby incorporated herein by reference, in its entirety.

Three paragraphs that begin with the first full paragraph on page 5 (which beings

with "It has previously") and end with the first full paragraph on page 6 (which begins with "Further illustration"):

It has previously been shown that prolactin, or substances that affect circulating prolactin levels, also affect circadian rhythms and in fact can be used to modify such rhythms (so that they more closely resemble the rhythms of lean, healthy, young individuals of the same sex) and to reset such rhythms (so that the modified rhythms persist in the modified condition). See, e.g. U.S. Patent Nos. 5,468,755; 5,585,347; 5,344,832; 5,496,803; 5,716,932; 5,716,993; 5,731,287; 5,679,685 and [Applications 08/158,153, 07/995,292, 07/719,745, 07/999,685 08/171,569, and U.S. Patent No.] 5,344,832. This prior work by the present inventors has been clinically tested in humans afflicted with various physiological disorders (obesity, diabetes, atherosclerosis, hypertension, immune dysfunction, and others) with meaningful results.

In particular, in U.S. Patent [Application Serial] No. 5,585,347 [07/995,292 (now allowed),] and in its continuation-in-part U.S. Pat. No. 5,830,895 [Serial No. 08/264,558, filed June 23, 1994], the present inventors disclose a method for the reduction in a subject, vertebrate animal or human, of body fat stores, and reduction of at least one of insulin resistance, hyperinsulinemia, and hyperglycemia, and other metabolic diseases, especially those associated with Type II diabetes. More specifically, the foregoing applications disclose methods for: (i) assessing the daily prolactin level cycles of a normal (healthy) human or vertebrate animal (free of obesity, disease or other disorder); (ii) diagnosing aberrant daily prolactin level cycles of a human or vertebrate animal; and (iii) determining the appropriate adjustments that need to be made to normalize such aberrant prolactin level cycles. This method involves the administration of at least one of a prolactin reducer and/or a prolactin enhancer at a first predetermined time (or times) within a 24-hour period (if only a prolactin reducer is administered) and/or at a second predetermined time (or times) of a 24-hour period (if a prolactin enhancer is administered). This therapy, when continued for several days, weeks or months, results in the long-term adjustment of aberrant or abnormal prolactin level cycles so that they conform to (or approach) normal prolactin level cycles. In most cases, this benefit persists over the long-term even after cessation of therapy. As a result, aberrant physiological parameters associated with various metabolic disorders are restored to normal levels or are modified to approach normal levels.

Further illustration of the utility of resetting prolactin rhythms can be found in

U.S. Patent [Application Serial] No. 5,696,128 [08/271,881, filed July 7, 1994], a method for regulating immune function by resetting prolactin rhythms is disclosed, and in U.S. Patent [Application Serial] No. 5,797,748 [08/475,296 filed June 7, 1995], a method for arresting the growth of or eradicating neoplastic growths in mammals having daily prolactin rhythms is disclosed.

IN THE CLAIMS

34. (Amended) A method for arresting the growth of or eradicating tumors in a mammal bearing one or more tumors comprising the steps of:

(a) comparing the daily plasma prolactin profile of said tumor bearing mammal to a normal daily prolactin profile for healthy mammals of the same species and sex;

(b) adjusting the daily plasma prolactin profile of said tumor bearing mammal by administering a prolactin enhancer or prolactin inhibitor at appropriate time intervals of day such that the adjusted daily plasma prolactin profile of [to] said tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy members of the same species and sex of said mammal;

(c) contacting the cells of said tumor with a benzophenoxazine-analog photosensitizer having phototoxicity against tumor cells; and

(d) exposing said contacted tumor cells to light, such that the growth of said tumor is retarded or said tumor is eradicated.

38. (Amended) The method of claim 37 wherein said melatonin or a pharmaceutically acceptable salt thereof is administered in an amount within the range of about 0.5 to about [asbout]20 mg/person/day.

54. (Amended) The method of claim [48] 43 wherein said benzophenoxazine analog is a member selected from the group consisting of 5-ethylamino-9-diethylamino-2-iodobenzo[a]phenothiaziniumchloride and 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride.